



Rejections Under 35 U.S.C. § 101

The Examiner rejects claims 54-67, 75-92, 102-107 and 115-175 under 35 U.S.C. § 101 alleging that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility.

More specifically, the Examiner contends:

It is clear from the instant specification that the vascular IBP-like growth factor described therein is what is termed an ‘orphan protein’ in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant’s claimed invention is incomplete.

Paper 20, page 3, third paragraph.

Applicants respectfully disagree and traverse.

First, Applicants respectfully point out that the principle of sequence relatedness or homology has, and is, being used by those of skill in the art to predict function based on sequence. In fact, advanced computer algorithms can detect statistically valid relationships among protein sequences even with similarity levels of roughly 20% identity between two or more sequences.¹ Indeed, recent commentators have noted that this form of biological research, termed “protein molecular biology,” is the direct consequence of the power of analytical algorithms. They found distinct thresholds for sequence, structure and function: at least 40% sequence identity corresponds to a sharing of precise function while sequence identities of about 25% comprise a functional class.² Thus, the Applicant’s prediction of VIGF activity based on a shared percent identity of 40-45% with the CCN family in the instant specification would be found credible by those skilled in the art.

Additionally, the Examiner’s assertion that “[t]here is absolutely no evidence of record or any line of reasoning that would support a conclusion that the vascular IBP-like

¹ Dunwell, et al., "Microbial Relatives of Seed Storage Proteins of Higher Plants: Conservation of Structure and Diversification of Function during Evolution of the Cupin Superfamily," *Microbiol. Mol. Biol. Rev.*, 64:153-79 (2000) Exhibit A.

² Wilson, C.A., et al, "Assessing Annotation Transfer to Genomics: Quantifying the relations between protein sequence, structure, and function through traditional and probabilistic scores," Department of Molecular Biophysics and Biochemistry, Yale University, *J. Mol. Biol.* 17:233-49, (2000) Exhibit B.

growth factor (VIGF) of the instant application can be used for wound healing and associated therapies, for enhancement of growth of vascular smooth muscle and endothelial cells, and therapeutically in ischemic tissues and for coronary stenosis" is in error. Consistent with Applicants' disclosure, Lassalle et al. independently confirmed VIGF (they call it ESM-1) as having endothelial and smooth muscle cell specific expression (see, e.g., Lassalle et al., J. Biol. Chem. 271:20458-64 (1996), Exhibit C). (Compare Figure 4 and pages 20460-61 of Lassalle et al. to Example 5 of the instant specification.) Similarly, they predict that VIGF participates in vascular cell biology and human lung physiology. (Compare Lassalle et al., abstract to the specification at page 4, lines 13-15.) It is well known in the art that vascular cell biology encompasses angiogenesis (i.e., the proliferation of vascular endothelial cells), while smooth muscle cells are critical to human lung physiology (see, e.g., James and Carroll, Eur. Respir. J. 15:782-9 (2000) abstract, Exhibit D; and Hanahan, Science 277:48-50 (1997), Exhibit E). Thus, the finding of Lassalle et al. support the statements and data disclosed in the originally filed specification, that VIGF can be used, for example, to enhance the growth of vascular smooth muscle and endothelial cells leading to the stimulation of angiogenesis (see, e.g., page 19, lines 7-9, and Example 5).

With regard to the rejection under 35 U.S.C. § 101, Applicants respectfully assert that the Examiner bears the burden of proof in order to demonstrate that the claimed invention lacks the asserted utility. *See*, Federal Register, December 21, 1999 (Volume 64, Number 244), Page 71442, § II, B, (2), (d), 3. This section states:

Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

Applicants respectfully assert that the Examiner's burden is not met by simply alleging that one of skill in the art would not find Applicants' assertion of utility credible, merely because "in the absence of a knowledge of the receptor to which VIGF binds, or the biological significance of this protein, there is no immediately obvious patentable use for it." As detailed above, the Examiner's contention of a lack of a specific and substantial credible

utility is not supported by the relevant art. Applicants have provided the Examiner with references demonstrating that: (1) Lassalle et al. independently identified VIGF and predict that VIGF participates in vascular cell biology and human lung physiology. (see, Lassalle et al., *supra*); and (2) that it is well known in the art that vascular cell biology encompasses angiogenesis (i.e., the proliferation of vascular endothelial cells), while smooth muscle cells are critical to human lung physiology (see, e.g., James and Carroll, *supra* and Hanahan, *supra*). Thus, the finding of Lassalle et al. supports the statements and data disclosed in the originally filed specification, that VIGF can be used, for example, to enhance the growth of vascular smooth muscle and endothelial cells leading to the stimulation of angiogenesis. (See, e.g., Hanahan). Thus, the Examiner's burden in evaluating utility is not met because it does not comport with what those in the art would reasonably believe.

Accordingly, Applicants respectfully submit that the Examiner has not met the burden required to reject claims 54-67, 75-92, 102-107 and 115-175 under 35 U.S.C. § 101. In contrast, Applicants assert that a person of ordinary skill in the art would readily comprehend the instant invention to have a specific, substantial, and credible utility as appropriately disclosed in the specification as originally filed. Applicants, therefore, respectfully assert that the rejection of claims 54-67, 75-92, 102-107 and 115-175 under 35 U.S.C. § 101 has been obviated and request that it be withdrawn.

Rejections Under 35 U.S.C. § 112

A. The Examiner rejects claims 54-67, 75-92, 102-107 and 115-175 under 35 U.S.C. § 112, first paragraph, allegedly for failing to adequately teach how to use the instant invention for reasons given with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully disagree with this rejection and traverse. As discussed above, the claimed polynucleotides have specific and substantial uses, for example, to enhance the growth of vascular smooth muscle and endothelial cells leading to the stimulation of angiogenesis (see, e.g., page 19, lines 7-9, and Example 5). Moreover, this immediate and specific utility is explicitly taught in the specification as filed. Accordingly, Applicants

respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

B. The Examiner further rejects claims 115-117 and 119-175 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

- i. The Examiner alleges that these claims are directed to new matter. Specifically, the Examiner contends:

The instant claims include the limitation of a nucleic acid encoding amino acids 30-44 of SEQ ID NO:2 and amino acids 55-69 of SEQ ID NO:2. Applicant points to page 6, lines 5-6 for support for these claim limitations. However, this portion of the specification only indicates that these are domains in the disclosed protein, and does not provide a basis for a claim to a nucleic acid comprising a nucleic acid encoding only these domains, absent evidence to the contrary.

Applicants respectfully disagree and traverse. Nonetheless, in an effort to facilitate prosecution, Applicants have amended claim 115 to remove the offending language, and cancelled claims 120 and 121, thereby obviating the rejection. Applicants reserve their rights to prosecute the subject matter of the claims prior to the amendment in subsequently filed applications. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

- ii. The Examiner further alleges that claims reciting (1) hybridization conditions; (2) percent identity; or (3) 30/50 contiguous nucleotides lack written description. The Examiner alleges that the specification does not convey to one skilled in the art that the inventors were in possession of any of the claimed sequences except for the explicitly disclosed SEQ ID NO:1. In particular, the Examiner argues that the specification does not describe a representative number of species, nor does the specification disclose any relevant identifying characteristics other than this nucleotide sequence.

Applicants respectfully disagree and traverse.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is discharged if the Examiner can present evidence or reasons why one skilled in the art would not reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, the Examiner has not met her burden.

Applicants submit that one skilled in the art could reasonably conclude that Applicants were in possession of the polynucleotides encompassed by the rejected claims in the present application as filed. Furthermore, Applicants submit that the Examiner has underestimated both the teaching of the present application and the level of skill in the art on the priority date of the present application.

As indicated by the Examiner, a claimed genus must be supported by a description of relevant identifying characteristics of a representative number of species. See, Written Description Guidelines at 71436; *Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998). What constitutes a "representative number of species" depends upon the knowledge and skill in the art. Moreover, such a description need not be of such specificity to provide support to claim each individual species encompassed by the genus. Rather, the description is deemed sufficient if it demonstrates to the skilled artisan that the Applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1405.

For example, in the claims reciting hybridization conditions, written description is clearly provided in the specification. (See, e.g., page 9, last full paragraph and Examples 4 and 5.) Once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the polynucleotide sequence and the hybridization conditions disclosed in the specification, the skilled artisan could readily envision any number of sequences that would hybridize to the claimed polynucleotide sequences. Hybridization techniques have

been around since the 1970s, and therefore because of the routine and well-known nature of these techniques, more than one representative number of species is not necessary.³

Thus, the specification clearly conveys that Applicants were in possession of the polynucleotides falling within the scope of claims reciting hybridization conditions on the priority date of the instant application.

Additionally, in the claims reciting "% identity," written description is explicitly provided in the specification. (See, page 10, lines 10-13; and page 12, lines 20-23.) Once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the polynucleotide and the polypeptide sequence of the present invention, the skilled artisan could readily envision any number of sequences that would be 90 or 95% identical to SEQ ID NO:1, 2, or the cDNA contained in ATCC Deposit No. 75874. For example, the skilled artisan could readily envision a countless number of polypeptide sequences, such as, for example, variants of SEQ ID NO:2 in which alterations to the sequence are made outside of the conserved CNN and IBP signature regions (*see, e.g.* specification pages 5, final paragraph through page 6, first full paragraph). Additionally, Applicants submit that "% identity" analysis has been around for over 15 years (*see, e.g.*, Pozdnyakov and Pankov, *Int J Pept Protein Res* 17:284-91 (1981); Wilbur and Lipman, *Proc Natl Acad Sci* 80:726-30 (1983); and Lipman and Pearson, *Science* 227:1435-41 (1985)), and therefore, because of the routine and well-known nature of these techniques, methods for identifying polynucleotides which fall within the scope of the "% identity" claims were conventional in the art on the priority date of the present invention.

Thus, the specification clearly conveys that Applicants were in possession of polynucleotides falling within the scope of claims reciting "% identity" on the priority date of the instant application.

Finally, claims reciting 30/50 contiguous nucleotides are fully described in the specification. (See, *e.g.*, page 10, lines 14-16). Once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the polynucleotide sequence disclosed in the specification, the skilled artisan could readily envision any number of sequences that would comprise 30/50 contiguous nucleotides of SEQ ID NO:1.

³ Applicants do point out that Examples 1 and 3-5 describe primers that hybridize to the present invention.

Additionally, Applicants respectfully remind the Examiner that just because the scope of such a claim is broad does not mean that the claim lacks written description. *See*, Written Description Guidelines, Comment 35. The Patent Office disagreed with several commentators who “advanced the position that disclosure of only a small fragment does not convey that the inventor was in possession of all of the possible molecules or that the inventor was in possession of the fragment wherever it occurs.” Instead, the PTO responded by stating:

The Office does not agree with the comment that the scope of such an EST claim is necessarily too large to satisfy the written description requirement. The PTO has issued numerous patents in the past directed to nucleic acids that use open-ended language. Although an applicant presenting an open-ended claim to an EST using open-ended claim language with disclosure of only the EST sequence is not in possession of any arbitrary specific possible molecule that contains the EST, the applicant may be in possession of a broad genus of DNA where the EST is in any random nucleic acid sequence.

Thus, even though the claims reciting 30/50 contiguous nucleotides may encompass a broad genus of polynucleotides which comprise the claimed 30/50 contiguous nucleotides, Applicants submit that they have met the written description requirement. Thus, the specification clearly conveys that Applicants were in possession of claims reciting 30/50 contiguous nucleotides on the priority date of the instant application.

Applicants point out that to support a written description rejection, the PTO has the burden of showing why the applicant’s evidence is insufficient. *See*, Written Description Guidelines at 71432, point 28. In any case where a lack of written description is found, the PTO should cite documentary evidence or technical reasoning to support the finding. *Id.* Applicants respectfully submit that the Examiner has not provided such evidence to show why one skilled in the art would not readily envisage the claims reciting hybridization conditions, “% identity” or 30/50 contiguous nucleotides.

For all of the above reasons, Applicants respectfully assert that the Examiner has failed to meet the burden in presenting evidence or reasons why those skilled in the art would not recognize the claimed invention from the disclosure. Moreover, Applicants respectfully assert that the Examiner will be unable to meet this burden because the specification conveys with reasonable clarity that Applicants were in possession of the claimed invention.

Therefore, Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Provisional Non-statutory Double Patenting

The Examiner provisionally rejected claims 115, 120-122, 135-149 and 162-175 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 08/196,362 (SEQ ID NO: 7788 and 7775), 08/346,731 (SEQ ID NO: 552), 08/420,856 (SEQ ID NO: 552), 08/221,623 (SEQ ID NO: 114), and 08/276,163 (SEQ ID NO: 15161).

Applicants take this opportunity to advise the Examiner that Applicants have cancelled all text in the above listed co-pending specifications relating to the above listed sequences, and cancelled all sequence listings relating to the above listed sequences, thereby obviating the rejection. Accordingly, Applicants respectfully request that the provisional rejection of claims 115, 120-122, 135-149 and 162-175 under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner provisionally rejected claims 115, 120-122, 135-149 and 162-175 under 35 U.S.C. § 102 (e) as being anticipated by copending Application No. 08/196,362 (SEQ ID NO: 7788 and 7775), 08/346,731 (SEQ ID NO: 552), 08/420,856 (SEQ ID NO: 552), 08/221,623 (SEQ ID NO: 114), and 08/276,163 (SEQ ID NO: 15161).

As mentioned above, Applicants advise the Examiner that Applicants have cancelled all text in the above listed co-pending specifications relating to the above listed sequences, and cancelled all sequence listings relating to the above listed sequences, thereby obviating the rejection. Accordingly, Applicants respectfully request that the provisional rejection of claims 115, 120-122, 135-149 and 162-175 under 35 U.S.C. § 102 (e) be reconsidered and withdrawn.

Conclusion

In view of the foregoing remarks, Applicants believe they have fully addressed the Examiner's concerns and that this application is now in condition for allowance. An early notice to that effect is urged. A request is made to the Examiner to call the undersigned at the phone number provided below if any further action by Applicants would expedite allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Enclosures
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